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A/C for Patents

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,070,877

Issued December 10, 1991

#33

Title: Novel Method of Myocardial Imaging

Inventors: Syed M. Mohiuddin and
Daniel E. Hilleman

Assignee: Medco Research Inc.

**REQUEST FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. §156
TRANSMITTAL LETTER**

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, D.C. 20231

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**OFFICE OF PETITIONS
A/C PATENTS**

Sir:

Submitted herewith is an original and a certified copy of a Request for Extension of the term of U.S. Patent 5,070,877:

Check number 0054222 for \$1,030.00 is enclosed as the fee for receiving and acting upon the application for extension.

The Commissioner is hereby authorized to charge payment of any additional processing fees during the pendency of this extension application or credit any overpayment to Deposit Account No. 01-0850. A duplicate copy of this cover letter is enclosed.

Respectfully submitted,

MEDCO RESEARCH, INC.

DATED: July 17, 1995

By


Jae H. Kim

Registration No. 32,907

Hopgood, Calimafde, Kalil & Judlowe

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Attorney for Assignee

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231

on July 17, 1995

Name Maria Alonso

Maria Alonso

Signature

July 17, 1995

Date of Signature

Express Mail Label No. TB907795526US

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,070,877

Issued December 10, 1991

Title: Novel Method of Myocardial Imaging

Inventors: Syed M. Mohiuddin and
Daniel E. Hilleman

Assignee: Medco Research Inc.

**REQUEST FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. §156**

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Pursuant to 35 U.S.C. § 156, Medco Research, Inc. (Medco), assignee of U.S. Patent No. 5,070,877 by an assignment from the inventors recorded on August 26, 1988 at Reel 4941, Frame 381-382, hereby requests an extension of the patent term for said Patent.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 and follows the numerical format and headings set forth in 37 C.F.R. § 1.740:

1. A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is adenosine (ADENOSCAN®), the package insert for which is attached as Exhibit 1. Adenosine is an endogenous nucleoside occurring in all cells of the body. It is prepared as a white crystalline powder. It is available in 30 ml vial as an intravenous infusion in ampules containing 3 mg adenosine per milliliter.

2. A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred under Section 505 of the Federal Food Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 355. Section 505 provides for the submission and approval of new drug applications (NDA's).

3. An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

Adenosine for Injection was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FFDCA on May

18, 1995. A copy of the letter from FDA announcing that approval is attached as Exhibit 2.

4. An identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing of use under FFDCA, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved.

The active ingredient in the approved product is adenosine. The chemical nomenclature of the product is 6-amino-9- β -ribofuranosyl-9-H-purine. Adenosine has been previously approved for commercial use under the FFDCA in a product identified as ADENOCARD® for use in the treatment of supraventricular tachycardia.

5. A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on May 18, 1995, and the last day within the sixty-day period permitted for submission of an application for extension of a patent is July 17, 1995. The date of submission of the present application is no later than July 17, 1995, and therefore, the present application has been timely filed.

6. The complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

Inventors: Syed M. Mohiuddin and Daniel E. Hilleman

U.S. Patent No. 5,070,877

Date of Issue: December 10, 1991

Date of Expiration: December 10, 2008

7. A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings.

A copy of the patent is attached as Exhibit 3.

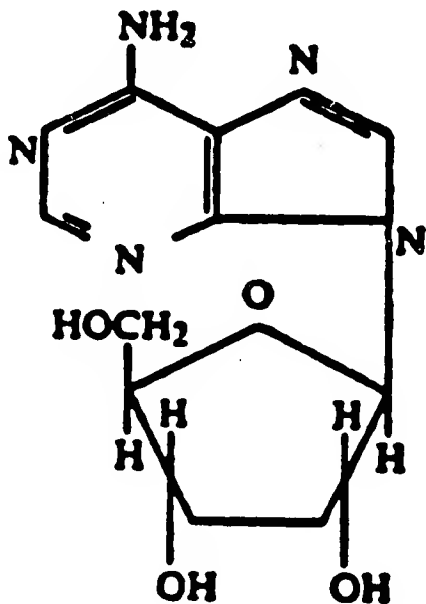
8. A copy of any disclaimer, certification of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

The first maintenance fee was paid on April 7, 1995 and a copy of the receipt of the maintenance fee payment is attached as Exhibit 4. No disclaimers, reexamination certificates, or certificates of correction have been issued for the patent.

9. A statement beginning on a new page that the patent claims the approved product or method of using or manufacturing the approved product, and a showing which lists each applicable patent and demonstrates the manner in which each applicable patent claim reads on the approved product as a method of using or manufacturing the approved product.

The approved product is identified as an adenosine receptor agonist in U.S.

Patent No. 5,070,877. The structure of the compound and its nomenclature are shown as follows:



6-amino-9-β-D-ribofuranosyl-9H-purine

U.S. Patent No. 5,070,877 claims a method of using adenosine, particularly for detecting and assessing the severity of myocardial dysfunction in a human, in Claims 1 to 48. These claims read as follows:

1. A method of detecting the presence and assessing the severity of myocardial dysfunction in a human comprising the steps of:
 - (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation; and
 - (b) performing a technique on said human to detect the presence and assess the severity of said myocardial dysfunction.
2. A method of detecting the presence and assessing the severity of myocardial dysfunction in a human comprising the steps of:
 - (a) administering by an intracoronary route to said human about 2 mcg to about 20 mcg of an adenosine receptor agonist sufficient to provide coronary artery dilation; and
 - (b) performing a technique on said human to detect the presence and assess the severity of said myocardial dysfunction.
3. The method of claim 1 or 2, wherein said myocardial dysfunction is selected from group consisting of coronary artery disease, ventricular dysfunction and differences in blood flow through disease free coronary vessels and stenotic coronary vessels.
4. The method of claim 1 or 2, wherein said adenosine receptor agonist is selected from the group consisting of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide-adenosine, cyclopentyl adenosine, 2-chloro adenosine, adenine, inosine, adenosine, monophosphate, adenosine diphosphate and adenosine triphosphate.
5. The method of claim 1 or 2, wherein said technique to detect the presence and assess the severity of myocardial dysfunction is selected from the group consisting of radiopharmaceutical myocardial perfusion imaging where said myocardial dysfunction is coronary artery disease, ventricular function imaging when said myocardial dysfunction is ventricular dysfunction and a method for measuring coronary blood flow velocity when said myocardial dysfunction is the difference in blood flow through disease free coronary vessels as opposed to stenotic coronary vessels.
6. The method of claim 1 wherein said adenosine receptor agonist is administered by intravenous infusion in a dosage of about 140 mcg/kg/minute.
7. The method of claims 1, 2, or 6 wherein said adenosine receptor agonist is adenosine.

8. The method of claim 3 wherein said adenosine receptor agonist is adenosine.
9. The method of claim 4 wherein said adenosine receptor agonist is adenosine.
10. The method of claim 1 wherein said radiopharmaceutical myocardial perfusion imaging is selected from the group consisting of scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET), nuclear magnetic resonance (NMR) imaging, perfusion contrast echocardiography, digital subtraction angiography (DSA) and ultrafast X-ray computer tomography (CINE CT).
11. The method of claim 10 wherein the radiopharmaceutical agent used in conjunction with said radiopharmaceutical myocardial perfusion imaging is selected from the group consisting of thallium-201, technetium-99m, derivatives of technetium-99m, nitrogen-13, rubidium-82, iodine-123 and oxygen-15.
12. The method of claim 11 wherein said radiopharmaceutical myocardial perfusion imaging technique is scintigraphy and said radiopharmaceutical agent is thallium-201.
13. The method of claim 5 wherein said ventricular function imaging technique is selected from the group consisting of echocardiography, contrast ventriculography and radionuclide angiography.
14. The method of claim 13 wherein said ventricular function imaging technique is echocardiography.
15. The method of claim 3 wherein said method for measuring coronary blood flow velocity is selected from the group consisting of doppler flow catheter, digital subtraction angiography and radiopharmaceutical imaging techniques.
16. The method of claim 15 wherein said method for measuring coronary blood flow velocity is doppler flow catheter.
17. A method of detecting the presence and assessing the severity of coronary artery disease in a human comprising the steps of:
 - (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation;
 - (b) administering a radiopharmaceutical agent into said human; and
 - (c) performing radiopharmaceutical myocardial perfusion imaging on said human in order to detect the presence and assess the severity of coronary artery disease.
18. The method of claim 17 wherein said adenosine receptor agonist is administered by intravenous infusion in a dosage of about 140 mcg/kg/minute.

19. A method of detecting the presence and assessing the severity of coronary artery disease in a human comprising the steps of:
 - (a) administering by an intracoronary route to said human about 2 mcg to about 20 mcg of an adenosine receptor agonist sufficient to provide coronary artery dilation;
 - (b) administering a radiopharmaceutical agent into said human; and
 - (c) performing radiopharmaceutical myocardial perfusion imaging on said human in order to detect the presence and assess the severity of coronary artery disease.
20. The method of claim 17 or 19, wherein said adenosine receptor agonist is selected from the group consisting of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide-adenosine, cyclopentyl adenosine, 2-chloro adenosine, adenosine, inosine, adenosine monophosphate, adenosine diphosphate and adenosine triphosphate.
21. The method of claim 17 or 19, wherein said radiopharmaceutical agent is selected from the group consisting of thallium-201, technetium-99m, derivatives of technetium-99m, nitrogen-13, rubidium-82, iodine-123 and oxygen-15.
22. The method of claim 17 or 19 wherein said radiopharmaceutical myocardial perfusion imaging is selected from the group consisting of scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET), nuclear magnetic resonance (NMR), imaging perfusion contrast echocardiography, digital subtraction angiography (DSA) and ultrafast X-ray computed tomography (CINE CT).
23. The method of claim 17, 19 or 18, wherein said adenosine receptor agonist is adenosine.
24. The method of claim 20 wherein said adenosine receptor agonist is adenosine.
25. The method of claim 21 wherein said radiopharmaceutical agent is thallium-201.
26. The method of claim 22 wherein said radiopharmaceutical myocardial perfusion imaging is scintigraphy.
27. A method of detecting the presence and assessing the severity of ventricular dysfunction caused by coronary artery disease, in a human, comprising the steps of:
 - (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation
 - (b) performing a ventricular function imaging technique on said human; and
 - (c) determining the presence and assessing the severity of ventricular dysfunction.

28. A method of detecting the presence and assessing the severity of ventricular dysfunction caused by coronary artery disease, in a human, comprising the steps of:
- (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation;
 - (b) performing a ventricular function imaging technique on said human; and
 - (c) determining the presence and assessing the severity of ventricular dysfunction.
29. The method of claim 27 or 28, wherein said adenosine receptor agonist is selected from the group consisting of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide-adenosine, cyclopentyl adenosine, 2-chloro adenosine, adenosine, inosine, adenosine monophosphate, adenosine diphosphate and adenosine triphosphate.
30. The method of claim 27 or 28, wherein said ventricular function imaging technique is selected from the group consisting of echocardiography, contrast ventriculography and radionuclide angiography.
31. The method of claim 27 wherein said adenosine receptor agonist is administered by intravenous infusion in a dosage of about 140 mcg/kg/minute.
32. The method of claim 27, 28 or 31, wherein said adenosine receptor agonist is adenosine.
33. The method of claim 29 wherein said adenosine receptor agonist is adenosine.
34. The method of claim 30 wherein said ventricular function imaging is technique is echocardiography.
35. A method of determining the difference between the coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human comprising the steps of:
- (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation;
 - (b) performing a method for measuring coronary blood flow velocity on said human in order to assess the vasodilatory capacity of disease free coronary vessels as opposed to stenotic coronary vessels.
36. The method of claim 35 wherein said adenosine receptor agonist is administered by intravenous infusion in a dosage of about 140 mcg/kg/minute.
37. A method of determining the difference between the coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human comprising the steps of:

- (a) administering by an intracoronary route to said human about 2 mcg to about 20 mcg of an adenosine receptor agonist sufficient to provide coronary artery dilation;
 - (b) performing a method for measuring coronary blood flow velocity on said human in order to assess the vasodilatory capacity (reserve capacity) of disease free coronary vessels as opposed to stenotic coronary vessels.
- 38. The method according to claim 35 or 37, wherein said adenosine receptor agonist is selected from the group consisting of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide-adenosine, cyclopentyl adenosine, 2-chloro adenosine, adenosine, inosine, adenosine monophosphate, adenosine diphosphate and adenosine triphosphate.
- 39. The method of claim 35 or 37, wherein said method for measuring coronary blood flow velocity is selected from the group of Doppler flow catheter, digital subtraction angiography and radiopharmaceutical imaging techniques.
- 40. The method of claim 35, 37 or 36, wherein said adenosine receptor agonist is adenosine.
- 41. The method of claim 38 wherein said adenosine receptor agonist is adenosine.
- 42. The method of claim 39 wherein said method for measuring coronary blood flow velocity is doppler flow catheter.
- 43. A method of detecting the presence and assessing the severity of coronary artery disease in a human comprising the steps of:
 - (a) administering to said human by intravenous infusion about 20 mcg/kg/minute to about 200 mcg/kg/minute of adenosine in order to provide coronary artery dilation;
 - (b) administering thallium-201 to said human; and
 - (c) performing the scintigraphy on said human in order to detect the presence and assess the severity of coronary artery disease.
- 44. A method of detecting the presence and assessing the severity of ventricular dysfunction in a human comprising the steps of:
 - (a) administering to said human by intravenous infusion about 20 mcg/kg/minute to about 200 mcg/kg/minute of adenosine in order to provide coronary artery dilation;
 - (b) performing an echocardiography on said human; and
 - (c) determining the presence and assessing the severity of ventricular dysfunction.
- 45. A method of determining the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human comprising the steps of:

- (a) administering to said human by intracoronary bolus injection about 2 mcg to about 20 mcg of adenosine, in order to provide coronary artery dilation;
 - (b) measuring the difference between coronary blood flow through disease-free coronary vessels and stenotic coronary vessels in said human using a doppler flow catheter in order to assess the vasodilatory capacity (reserve capacity) of disease-free coronary vessels as opposed to stenotic coronary vessels.
46. A method of detecting the presence and assessing the severity of coronary artery disease in a human comprising the steps of:
- (a) administering to said human by intracoronary bolus injection about 2 mcg to about 200 mcg of adenosine in order to provide coronary artery dilation;
 - (b) administering thallium-201 to said human; and
 - (c) performing scintigraphy on said human in order to detect the presence and assess the severity of coronary artery disease.
47. A method of detecting the presence and assessing the severity of ventricular dysfunction in a human comprising the steps of:
- (a) administering to said human by intracoronary bolus injection about 2 mcg to about 20 mcg of adenosine in order to provide coronary artery dilation;
 - (b) performing an echocardiography on said human; and
 - (c) determining the presence and assessing the severity of ventricular dysfunction.
48. A method of determining the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human comprising the steps of:
- (a) administering to said human by intravenous infusion about 20 mcg/kg/minute to about 200 mcg/kg/minute of adenosine, in order to provide coronary artery dilation;
 - (b) measuring the difference between coronary blood flow through disease-free coronary vessels and stenotic coronary vessels in said human using a Doppler flow catheter in order to assess the vasodilatory capacity (reserve capacity) of disease-free coronary vessels as opposed to stenotic coronary vessels.

10. A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follow:
-

- (i) For a patent that claims a human drug product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number; and the date on which the NDA was approved.

The Investigational New Drug Application (IND 30,974) for the use of adenosine in the detection and assessing the severity of myocardial infarction was filed with the Food and Drug Administration (FDA) by Medco Research, Inc. on December 9, 1987 and became effective on December 10, 1987.

The New Drug Application (NDA 20-059) was filed on February 9, 1990 by Medco Research, Inc. for the detection and assessment of the severity of myocardial infarction in humans.

New Drug Application NDA 20-059 was approved by the FDA on May 18, 1995.

11. A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

A brief description of the activities undertaken by the Applicant Medco Research, Inc. during the applicable regulatory review period is attached as Exhibit 5. Exhibit 5 contains a chronology of the major events in the testing of adenosine by Medco Research, Inc. and communications between Medco Research, Inc. and FDA from December 9, 1987 to May 18, 1995.

12. A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.
-

Applicant is of the opinion that U.S. Patent No. 5,070,877 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

(a) U.S. Patent No. 5,070,877 claims a method of use of a pharmaceutical compound which is a product (35 U.S.C. § 156 (a)(1)).

(b) The term of U.S. Patent No. 5,070,877 has not expired (35 U.S. C. § 156 (a)(1)).

(c) The term of U.S. Patent No. 5,070,877 has never been extended before submission of this application (35 U.S.C. § 156 (a)(2)).

(d) This application is being submitted by the authorized agent of the owner of record of the patent in accordance with the requirements of 35 U.S.C. § 156 (d) and the rules of the United States Patent and Trademark Office (35 U.S.C. § 156 (a)(5)(A) and 37 C.F.R. §1.740).

(e) This product, adenosine, and the use of it, has been subjected to a regulatory review period before its commercial marketing or use (35 U.S.C. § 156 (a)(4)).

(f) The commercial marketing or use of the product after the regulatory review period will be the first permitted commercial marketing or use of the product under Section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355 (35 U.S.C. § 156 (a)(5)(A)).

(g) No other patent has been extended for the same regulatory review period for the product adenosine used in accordance with the claims of U.S. 5,070,877 (35 U.S.C. § 156 (c)(4)).

The length of extension of the patent term for U.S. Patent No. 5,070,877 claimed by Applicant is 159 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.775, as follows:

(a) Pursuant to 37 C.F.R. § 1.775 (c) the regulatory review period under 35 U.S.C. §156 (g)(1)(B) began on December 10, 1987 and ended on May 18, 1995, which is the total of 2,716 days. This is the sum of the two phases described below:

(i) The "Testing Phase" under 35 U.S.C. § 156 (g)(1)(B)(i) began on December 10, 1987, and ended on February 9, 1990, which is 792 days; and

(ii) The "Application Phase" under 35 U.S.C. § 156 (g)(1)(B) began on February 14, 1990 and ended on May 18, 1995, which is 1,919 days.

(b) Pursuant to 37 C.F.R. § 1.775(d), the length of the patent term extension is calculated as follows:

(1) The following number of days are to be subtracted from the regulatory review period:

(i) The number of days in the regulatory review period which were on or before the date on which the patent was issued, December 10, 1991, which is 1,461 days, and

(ii) The number of days in the regulatory review period during which Applicant did not act with due diligence, which (after the date of patent issuance) is zero (0) days, and

(iii) One-half the number of days in the Testing Phase after the patent issued, which is zero (0) days;

(2) The remaining total of 1,255 days, which added to the original term of the patent, which expires December 10, 2008, would provide an exclusive marketing period lasting until May 18, 2012.

(3) Fourteen (14) years, when added to the date of NDA approval, May 18, 1995, would result in the date May 18, 2009.

(4) The earlier date of those in paragraphs (2) and (3) above is May 18, 2009.

(5) Because the patent was issued after September 24, 1984, one must add five (5) years to the expiration date of the patent, leading to the date December 10, 2013.

(6) The earlier date of those is paragraphs (4) and (5) is May 18, 2009, and thus that is the date to which the patent term should be extended.

Therefore, Applicant is requesting an extension of the patent term of 159 days to May 18, 2009.

13. A statement that applicant acknowledges a duty to disclose to the commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patent and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

In addition to the information provided above, Applicant notes that U.S. Patent No. 4,673,563, entitled "Adenosine in the Treatment of Supraventricular Tachycardia" which issued on June 16, 1987 was filed on April 8, 1985, as U.S. Serial No. 721,122, and was a continuation of U.S. Serial No. 452,014, filed December 21, 1982, now abandoned which was a continuation-in-part of Serial No. 190,052, filed October 14, 1980, now U.S. 4,304,922. The product is approved for commercial use under the FFDCA and sold under the trademark ADENOCARD.

14. The prescribed fee for receiving and acting upon the application for extension.

A check in the amount of \$1,030.00 is enclosed with this application.

15. The name, address and telephone number of the person to whom inquires and correspondence relating to the application for patent term extension are to be directed.

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16. A duplicate of the application papers certified as such.

A certified copy is submitted herewith.

17. An oath or declaration as set forth in paragraph (b) of 37 C.F.R. § 1.740.

I, Jae H. Kim, declare that:

1) I am a patent attorney authorized to practice before the United States Patent and Trademark Office (Registration No. 32,907) and have general authority from Medco Research, Inc., owner of U.S. Patent No. 5,070,877, to act on its behalf;

2) I have reviewed and understand the contents of this application;

3) I believe that the patent is subject to extension pursuant to 37 C.F.R. § 1.740;

4) I believe that an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

5) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 5,070,877.

Respectfully submitted,

MEDCO RESEARCH, INC.

Dated: July 17, 1995

By 

Jae H. Kim

Registration No. 32,907

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Attorney for Assignee

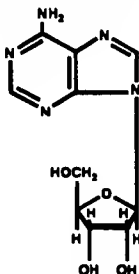
ADENOSCAN®

adenosine

For Intravenous Infusion Only

DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 8-amino-9-beta-D-ribofuranosyl-9-H-purine and has the following structural formula:



C₁₀H₁₃N₅O₄ 267.24
Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH of the solution.

Each Adenoscan vial contains a sterile, non-pyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in Water for Injection, q.s. The pH of the solution is between 4.5 and 7.5.

CLINICAL PHARMACOLOGY:

Mechanism of Action

Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine is thought to exert its pharmacological effects through activation of purine receptors (cell-surface A₁ and A₂ adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylyl cyclase through A₂ receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive.

Myocardial uptake of thallium-201 is directly proportional to coronary blood flow. Since Adenoscan significantly increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, Adenoscan causes relatively less thallium-201 uptake in vascular territories supplied by stenotic coronary arteries; i.e., a greater difference is seen after Adenoscan between areas served by normal and areas served by stenotic vessels than is seen prior to Adenoscan.

Hemodynamics

Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart, presumably due to A₁-receptor agonism, and produces peripheral vasodilation, presumably due to A₂-receptor agonism. The net effect of Adenoscan in humans is typically a mild to moderate reduction in systolic, diastolic and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have been observed.

Pharmacokinetics

Intravenously administered adenosine is rapidly cleared from the circulation via cellular uptake, primarily by erythrocytes and vascular endothelial cells. This process involves a specific transmembrane nucleoside carrier system that is reversible, nonconcentrative, and bidirectionally symmetrical. Intracellular adenosine is rapidly metabolized either via phosphorylation to adenosine monophosphate by adenosine kinase, or via deamination to inosine by adenosine deaminase in the cytosol. Since adenosine kinase has a lower K_m and V_{max} than adenosine deaminase, deamination plays a significant role only when cytosolic adenosine saturates the phosphorylation pathway. Inosine formed by deamination of adenosine can leave the cell intact or can be degraded to hypoxanthine, xanthine, and ultimately uric acid. Adenosine monophosphate formed by phosphorylation of adenosine is incorporated into the high-energy phosphate pool. While extracellular adenosine is primarily cleared by cellular uptake with a half-life of less than 10 seconds in whole blood, excessive amounts may be deaminated by an ecto-form of adenosine deaminase. As Adenoscan requires no hepatic or renal function for its activation or inactivation, hepatic and renal failure would not be expected to alter its effectiveness or tolerability.

Clinical Trials

In two crossover comparative studies involving 319 subjects who could exercise (including 108 healthy volunteers and 213 patients with known or suspected coronary disease), Adenoscan and exercise thallium images were compared by blinded observers. The images were concordant for the presence of perfusion defects in 85.5% of cases by global analysis (patient by patient) and up to 93% of cases based on vascular territories. In these two studies, 193 patients also had recent coronary arteriography for comparison (healthy volunteers were not catheterized). The sensitivity (true positive Adenoscan divided by the number of patients with positive (abnormal) angiography) for detecting angiographically significant disease (≥50% reduction in the luminal diameter of at least one major vessel) was 64% for Adenoscan and 64% for exercise testing, while the specificity (true negative divided by the number of patients with negative angiogram) was 54% for Adenoscan and 65% for exercise testing. The 95% confidence limits for Adenoscan sensitivity were 56% to 78% and for specificity were 37% to 71%.

Intracoronary Doppler flow catheter studies have demonstrated that a dose of intravenous Adenoscan of 140 mcg/kg/min produces a maximum coronary hyperemia (relative to intracoronary papaverine) in approximately 95% of cases within two to three minutes of the onset of the infusion. Coronary blood flow velocity returns to basal levels within one to two minutes of discontinuing the Adenoscan infusion.

INDICATIONS AND USAGE:

Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately. (See WARNINGS).

CONTRAINDICATIONS:

Intravenous Adenoscan (adenosine) should not be administered to individuals with:

1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).
3. Known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma).
4. Known hypersensitivity to adenosine.

WARNINGS:

Fatal Cardiac Arrest, Life Threatening Ventricular Arrhythmias, and Myocardial Infarction.

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk.

Sinoatrial and Atrioventricular Nodal Block

Adenoscan (adenosine) exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia. Approximately 8.3% of patients develop AV block with Adenoscan, including first-degree (2.9%), second-degree (2.6%) and third-degree (0.6%) heart block. All episodes of AV block have been asymptomatic, transient, and did not require intervention. Adenoscan can cause sinus bradycardia. Adenoscan should be used with caution in patients with pre-existing first-degree AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). Adenoscan should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. Sinus pause has been rarely observed with adenosine infusions.

Hypotension

Adenoscan (adenosine) is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflex mechanism are able to maintain blood pressure and tissue perfusion in response to Adenoscan by increasing heart rate and cardiac output. However, Adenoscan should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia, due to the risk of hypotensive complications in these patients. Adenoscan should be discontinued in any patient who develops persistent or symptomatic hypotension.

Hypertension

Increases in systolic and diastolic pressure have been observed (as great as 140 mm Hg systolic in one case) concomitant with Adenoscan infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction

Adenoscan (adenosine) is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (V_E) and reduce arterial PCO₂, causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnea) or an urge to breathe deeply with Adenoscan. These respiratory complaints are transient and only rarely require intervention.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenoscan has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenoscan should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g., asthma). Adenoscan should be discontinued in any patient who develops severe respiratory difficulties.

PRECAUTIONS:

Drug Interactions

Intravenous Adenoscan (adenosine) has been given with other cardiovascular drugs (such as beta adrenergic blocking agents, cardiac glycosides, and calcium channel blockers) without apparent adverse interactions, but its effectiveness with these agents has not been systematically evaluated. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, Adenoscan should be used with caution in the presence of these agents.

The vasoactive effects of Adenoscan are inhibited by adenosine receptor antagonists, such as alkylxanthines (e.g., caffeine and theophylline). The safety and efficacy of Adenoscan in the presence of these agents has not been systematically evaluated.

The vasoactive effects of Adenoscan are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of Adenoscan in the presence of dipyridamole has not been systematically evaluated.

Whenever possible, drugs that might inhibit or augment the effects of adenosine should be withheld for at least five half-lives prior to the use of Adenoscan.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential of Adenoscan (adenosine). Adenosine was negative for genotoxic potential in the Salmonella (Ames Test) and Mammalian Microsome Assay.

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. In rats and mice, adenosine administered intravenously once daily for five days at 50, 100, and 150 mg/kg (110, 220, and 330 mg/m²) (rats) and 5-15 (mice) times human dosage on a mg/m² basis, caused decreased spermatogenesis and increased numbers of abnormal sperm, a reflection of the ability of adenosine to produce chromosomal damage.

Pregnancy Category C

Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. Because it is not known whether Adenoscan can cause fetal harm when administered to pregnant women, Adenoscan should be used during pregnancy only if clearly needed.

Pediatric Use

The safety and effectiveness of Adenoscan in patients less than 18 years of age have not been established.

ADVERSE REACTIONS:

The following reactions with an incidence of at least 1% were reported with intravenous Adenoscan among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of Adenoscan but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

Exhibit 1

Flushing	44%
Chest discomfort	40%
Dyspnea or urge to breathe deeply	28%
Headache	16%
Throat, neck or jaw discomfort	15%
Gastrointestinal discomfort	13%
Lightheadedness/dizziness	12%
Upper extremity discomfort	4%
ST segment depression	3%
First-degree AV block	3%
Second-degree AV block	3%
Paresthesia	2%
Hypotension	2%
Nervousness	2%
Arrhythmias	1%

Adverse experiences of any severity reported in less than 1% of patients include:

Body as a Whole: back discomfort; lower extremity discomfort; weakness.

Cardiovascular System: nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause; sweating; T-wave changes, hypertension (systolic blood pressure > 200 mm Hg).

Central Nervous System: drowsiness; emotional instability; tremors.

Genital/Urinary System: vaginal pressure; urgency.

Respiratory System: cough.

Special Senses: blurred vision; dry mouth; ear discomfort; metallic taste; nasal congestion; scotomas; tongue discomfort.

OVERDOSAGE:

The half-life of Adenosine is less than 10 seconds and side effects of Adenoscan (when they occur) usually resolve quickly when the infusion is discontinued, although delayed or persistent effects have been observed. Methyloxanthines, such as caffeine and theophylline, are competitive adenosine receptor antagonists and theophylline has been used to effectively terminate persistent side effects. In controlled U.S. clinical trials, theophylline (50-125 mg slow intravenous injection) was needed to abort Adenoscan side effects in less than 2% of patients.

DOSAGE AND ADMINISTRATION:

For intravenous infusion only.

Adenoscan should be given as a continuous peripheral intravenous infusion.

The recommended intravenous dose for adults is 140 mcg/kg/min infused for six minutes (total dose of 0.84 mcg/kg).

The required dose of thallium-201 should be injected at the midpoint of the Adenoscan infusion (i.e., after the first three minutes of Adenoscan). Thallium-201 is physically compatible with Adenoscan and may be injected directly into the Adenoscan infusion set.

The injection should be as close to the venous access as possible to prevent an inadvertent increase in the dose of Adenoscan (the contents of the IV tubing) being administered.

There are no data on the safety or efficacy of alternative Adenoscan infusion protocols.

The safety and efficacy of Adenoscan administered by the intracoronary route have not been established.

The following Adenoscan infusion nomogram may be used to determine the appropriate infusion rate corrected for total body weight:

Patient Weight		Infusion Rate mL/min
kg	lbs	
45	99	2.1
50	110	2.3
55	121	2.6
60	132	2.8
65	143	3.0
70	154	3.3
75	165	3.5
80	176	3.8
85	187	4.0
90	198	4.2

This nomogram was derived from the following general formula:

$$\frac{0.140 \text{ (mg/kg/min)} \times \text{total body weight (kg)}}{\text{Adenoscan concentration (3 mg/mL)}} = \text{infusion rate (mL/min)}$$

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED:

Adenoscan (adenosine) is supplied as a 30 mL vial of sterile nonpyrogenic solution in normal saline.

NDC 0489-0871-30

Product Code 67130

90 mg/30 mL (3 mg/mL) in a 30 mL single-dose, flip-top glass vial, packaged individually and in packages of ten.

Store at controlled room temperature 15°-30°C (59°-86°F).

Do not refrigerate as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use.

Contains no preservative. Discard unused portion.

CAUTION: Federal law prohibits dispensing without prescription.

Fujisawa USA, Inc.
Deerfield, IL 60015
Under license from Medco Research, Inc.
Research Triangle Park, NC 27709

45558B/Issued May 1995

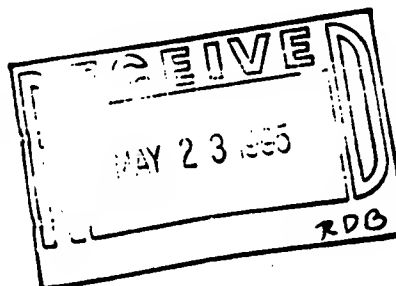
CONFIDENTIAL

NDA 20-059

Food and Drug Administration
Rockville MD 20857

MAY 18 1995

Medco Research, Inc.
Attention: Roger Blevins, Pharm.D.
P.O. Box 13886
85 TW Alexander Drive
Suite 200
Research Triangle Park, NC 27709



Dear Dr. Blevins:

Please refer to your February 9, 1990 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adenoscan (adenosine) Injection.

We acknowledge receipt of your amendments dated April 24 and 25 and May 5 and 16, 1995.

This new drug application provides for use of Adenoscan as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the April 24, 1995 draft labeling with the following revisions:

1. Please change the title of the Carcinogenesis, Mutagenesis section to read **Carcinogenesis, Mutagenesis, Impairment of Fertility**.
2. Under the Carcinogenesis, Mutagenesis, Impairment of Fertility section, please change the second sentence of the second paragraph to read:

in rats and mice, adenosine administered intraperitoneally once a day for five days at 50, 100, and 150 mg/kg [10-30 (rats) and 5-15 (mice) times human dosage on a mg/M² basis] caused decreased spermatogenesis and increased numbers of abnormal sperm, a reflection of the ability of adenosine to produce chromosomal damage.

CONFIDENTIAL

3. Under **WARNINGS**, please change the first subsection to read:

**Fatal Cardiac Arrest, Life Threatening
Ventricular Arrhythmias, and Myocardial
Infarction**

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk.

Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the April 24, 1995 draft labeling with the noted revisions. Marketing the product with FPL that is not identical to this revised draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-059. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

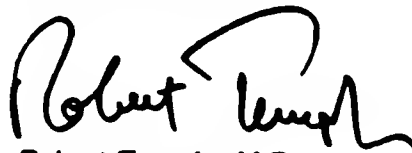
Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Diana Willard
Consumer Safety Officer
(301) 594-5300

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

United States Patent [19]

Mohiuddin et al.

[11] Patent Number: 5,070,877

[45] Date of Patent: Dec. 10, 1991

[54] **NOVEL METHOD OF MYOCARDIAL IMAGING**

[75] Inventors: Syed M. Mohiuddin; Daniel E. Hilleman, both of Omaha, Nebr.

[73] Assignee: McDeco Research, Inc., Los Angeles, Calif.

[21] Appl. No.: 330,156

[22] Filed: Mar. 29, 1989

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 231,217, Aug. 11, 1988, abandoned.

[51] Int. Cl.³ A61B 6/00

[52] U.S. Cl. 128/653.4; 600/4; 424/9; 514/46; 128/654

[58] Field of Search 600/3, 4; 128/659 C; 424/9; 514/46, 47

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Primary Examiner—C. Fred Rosenbaum

Assistant Examiner—Mark O. Polutta

Attorney, Agent, or Firm—Pennie & Edmonds

[57] **ABSTRACT**

The parenteral use of adenosine, functional adenosine receptor agonists which include 1-methyl-2-phenylethyladenosine, 5-ethyl carboxamide adenosine, cyclopentyl adenosine and 2-chloro adenosine; metabolic precursors or by-products of adenosine which include adenine and inosine; and phosphorylated derivatives of adenosine including adenosine monophosphate, adenosine diphosphate and adenosine triphosphate in conjunction with various invasive and noninvasive diagnostic techniques to detect the presence or assess the severity of vascular disease is a novel application (indication) for these compounds and forms the basis of this patent application.

48 Claims, No Drawings

NOVEL METHOD OF MYOCARDIAL IMAGING

This application is a continuation-in-part of application Ser. No. 231,217 filed Aug. 11, 1988 now abandoned.

BACKGROUND OF THE INVENTION

Several invasive and noninvasive techniques are used to assess patients with known or suspected coronary artery disease. Included among the noninvasive methodologies are electrocardiography, radionuclide angiography (first pass and equilibrium studies utilizing, for example, technecium 99 m labeled red blood cells), myocardial perfusion scintigraphy (utilizing positron emitting radiopharmaceuticals, for example, thallium-201, rubidium-82, nitrogen-13), and echocardiography (M mode and two dimensional). The manifestations of coronary artery disease are a function of the balance between myocardial oxygen supply and demand. Although these noninvasive procedures may be performed in a resting subject, there may not be sufficient imbalance between supply and demand to detect abnormalities at rest. Therefore, provocative studies are frequently performed to improve the predictive accuracy of these diagnostic procedures. The most commonly employed provocative (stress) technique utilizes a standard exercise protocol. Under conditions of exercise myocardial oxygen demand is increased to exceed supply. This form of stress testing is commonly employed in conjunction with electrocardiography, radionuclide angiography, myocardial perfusion scintigraphy, echocardiography, and contrast ventriculography.

Recently, provocative studies have been developed utilizing pharmacological techniques designed to increase myocardial oxygen supply. Specifically, coronary vasodilators (e.g. nitrates, papavarine, dipyridamole, etc.) have been used for this purpose, although none have been approved by the FDA for this specific indication. While the mechanism is not clear, these agents may dilate normal vessels to a greater extent than diseased vessels, establishing a shunt or "myocardial steal". Pharmacological provocation may be particularly useful in patients who are unable to exercise, and may be equal to or superior to exercise provocation in patients capable of exercising. Furthermore, since exercise increases demand and coronary vasodilators increase supply, it is possible that the highest diagnostic yield will accrue when they are used in conjunction with one another.

Coronary arteriography is an invasive procedure which currently represents the "gold standard" for confirming the diagnosis of coronary artery disease. However, this procedure only establishes the anatomical severity of the disease and provides little information concerning the functional significance of visible lesions. Furthermore, small vessel disease may be present and beyond the resolution of currently available equipment. Recently, in an attempt to establish the functional significance of coronary lesions, coronary vasodilators have been administered by intracoronary injection or intravenous infusion and coronary blood flow is measured by one of several techniques, such as doppler flow catheters, videodensitometry, coronary sinus thermolulution, and radionuclide clearance of inert gases. These techniques are becoming more widely used to measure coronary flow reserve (i.e. reserve capacity) which provides important information concerning the

functional significance of stenotic vessels. Although nitrates, papavarine, and dipyridamole have been used by some physicians for this purpose, no vasodilator has been approved by the FDA for this specific indication. The use of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide adenosine, cyclopentyl adenosine 2-chloro adenosine, adenine, inosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate, in conjunction with the above stated techniques to measure coronary flow reserve and assess the functional severity of stenotic vessels represents a novel application (indication) of our compound.

SUMMARY OF THE INVENTION

Briefly, the present invention comprises a method of detecting the presence or assessing the severity of vascular disease which includes the administration to the human host of an effective dilating amount of adenosine; functional adenosine receptor agonists (e.g., 1-methyl-2-phenylethyladenosine, 5-ethyl carboxamide adenosine, cyclopentyl adenosine or 2-chloro adenosine); metabolic precursors or byproducts of adenosine (e.g., adenine and inosine); and phosphorylated derivatives of adenosine (e.g., adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate), in conjunction with invasive or noninvasive techniques.

It is an object of this invention to provide a new diagnostic method to aid in the determination of the extent and severity of heart disease.

It is a further object of this invention to provide a new radioimaging technique for the coronary arteries.

More particularly, it is one object of this invention to provide an improved method of radioimaging the coronary arteries.

It is one significant object of this invention to provide wash out times for the radiolabeled agents used in stress-free cardiac imaging which are comparable to the wash out times presently attainable only in stress or exercise radioimaging tests.

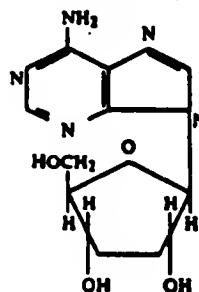
These and other objects and advantages will be apparent from the more detailed description which follows.

DETAILED DESCRIPTION OF THE INVENTION

Adenosine is chemically designated as 9- β -D-ribofuranosyl-9H-purine-6-amine; 6-amino-9- β -D-ribofuranosyl-9H-purine; 9- β -D-ribofuranosidoadenine; adenine riboside.

Adenosine is a nucleoside widely distributed in nature, factured from yeast nucleic acid. It is practically insoluble in alcohol. Crystals form from water, mp 234°-235°. $[\alpha]_D^{25} - 61.7^\circ$ (c=0.706 in water; $[\alpha]_D^{25} - 58.2^\circ$ (c=658 in water). uv max: 260 nm (ϵ 15,100).

The structural formula is as follows:



-continued

$C_{10}H_{13}N_5O_4$ 267.24
Empirical Formula Molecular Weight

This invention utilized adenosine administration as a pharmacological stressor in conjunction with any one of several noninvasive diagnostic procedures available. For example, intravenous adenosine may be used in conjunction with thallium-201 myocardial perfusion imaging to assess the severity of myocardial ischemia. In this case, any one of several different radiopharmaceuticals may be substituted for thallium-201 (e.g. rubidium-82, technetium 99m, derivatives of technetium 99m, nitrogen-13, iodine 123, etc.). Similarly, adenosine may be administered as a pharmacological stressor in conjunction with radionuclide angiography to assess the severity of myocardial dysfunction. In this case, radionuclide angiographic studies may be first pass or gated equilibrium studies of the right and/or left ventricle. Similarly, adenosine may be administered as a pharmacological stressor in conjunction with echocardiography to assess the presence of regional wall motion abnormalities. Similarly, adenosine may be administered as a pharmacological stressor in conjunction with invasive measurements of coronary blood flow such as by intracardiac catheter to assess the functional significance of stenotic coronary vessels.

This invention typically involves the administration of adenosine by intravenous infusion in doses which are effective to provide coronary artery dilation (approximately 20-200 mcg/kg/min). However, its use in the invasive setting may involve the intracoronary administration of the drug in bolus doses of 2-20 mcg. The adenosine used in this invention is normally admixed with any pharmaceutically suitable carrier or carriers such as saline, dextrose, water, or any other carrier customarily used for the type of administration intended. The solution may contain the active ingredient in a widely varying amount, for example, from about 1 mg/ml to about 12 mg/ml.

These doses increase coronary flow approximately 4-5 times resting values. Unlike papavarine which in this setting frequently causes QT interval prolongation, significant electrocardiographic or systemic hemodynamic abnormalities have not been observed. Adenosine is a superior vasodilator for this purpose.

The practice of this invention is applicable to radiopharmaceuticals generally, and specifically to those mentioned hereinabove.

Contemplated as equivalents of adenosine in the practice of this invention are analogues, derivatives, metabolic precursors or by-products or conjugates intended to function as agonists of the adenosine receptor responsible for mediating vasodilation. This appears to be the A_2 receptor subtype. Several analogues of adenosine have been developed which appear to have greater affinity or specificity for the A_2 receptor. These include primarily the N_6 substituted derivatives and the 2-carbon derivatives such as 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide adenosine, cyclopentyl adenosine, 2-chloro adenosine, etc.

The following methods are preferred embodiments of our invention.

The method comprising the use of an agent which is adenosine, functional adenosine receptor agonists, metabolic precursors or by-products of adenosine, or phosphorylated derivatives of adenosine as a substitute for exercise in conjunction with myocardial perfusion im-

aging to detect the presence and/or assess the severity of coronary artery disease in humans wherein myocardial perfusion imaging is performed by any one of several techniques including radiopharmaceutical myocardial perfusion imaging, planar (conventional) scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET), nuclear magnetic resonance (NMR) imaging, perfusion contrast echocardiography, digital subtraction angiography (DSA), or ultrafast x-ray computed tomography (CINE CT).

The method comprising the use of an agent which is adenosine, functional adenosine receptor agonists, metabolic precursors or by-products of adenosine, or phosphorylated derivatives of adenosine as a substitute for exercise in conjunction with imaging to detect the presence and/or assess the severity of ischemic ventricular dysfunction in humans wherein ischemic ventricular dysfunction is measured by any one of several imaging techniques including echocardiography, contrast ventriculography, or radionuclide angiography.

The method comprising the use of an agent which is adenosine, functional adenosine receptor agonists, metabolic precursors or by-products of adenosine, or phosphorylated derivatives of adenosine as a coronary hyperemic agent in conjunction with means for measuring coronary blood flow velocity to assess the vasodilatory capacity (reserve capacity) of coronary arteries in humans wherein coronary blood flow velocity is measured by any one of several techniques including Doppler flow catheter, digital subtraction angiography or other radiopharmaceutical imaging technique.

The following Examples are to illustrate the invention, and are not intended to limit the invention.

EXAMPLE I

As set forth in this example, the effects of intravenous adenosine as a pharmacological stressor in conjunction with thallium 201 scintigraphy were evaluated. In the first set of experiments, adenosine was compared to exercise in a crossover study design using planar (conventional) thallium 201 scintigraphy in a population of 20 healthy normal volunteers. In the second set of studies, adenosine was compared to dipyridamole in a crossover study design using planar (conventional) thallium 201 scintigraphy in a population of 26 subjects (12 healthy volunteers and 14 patients with angiographically documented coronary artery disease). In the third set of experiments, adenosine was evaluated using thallium 201 single-photon emission computed tomography (SPECT) in a population of 33 patients (18 normal subjects and 15 patients with angiographically documented coronary artery disease).

In the first set of experiments, 20 healthy normal volunteers (age 19-39 years) underwent planar (conventional) stress/redistribution thallium 201 scintigraphy twice (in a random crossover design). One study employed maximum treadmill exercise (Bruce protocol) as the method of stress and the other study employed an intravenous infusion of adenosine as the method of stress. Heart rate, blood pressure and a 12-lead electrocardiogram were monitored throughout the study. The exercise stress test was conducted in standard fashion. The adenosine stress test employed a constant infusion of adenosine initiated at 20 mcg/kg/min. The infusion was doubled at intervals to a maximum dose of 140 mcg/kg/min. The maximum tolerable dose was admin-

istered for at least 5 minutes prior to a single bolus injection of thallium 201 (approximately 2.0 mCi). Early (stress) imaging was performed 5-10 minutes after the thallium injection and delayed (redistribution) imaging was performed 3-4 hours after thallium injection. The adenosine infusion was continued to the end of early imaging. Early and delayed imaging each consisted of 3 sets of images (left anterior oblique, anterior and left lateral projections). The images were acquired and reconstructed in standard fashion. The adenosine infusion was well tolerated in all subjects. The exercise stress images and the adenosine stress images were interpreted as normal (i.e., no perfusion defect detected) in all subjects. This experiment indicates that adenosine compares favorably to exercise in detecting normalcy by planar thallium 201 scintigraphy.

In the second set of experiments, 12 healthy normal volunteers and 14 patients with angiographically documented coronary artery disease underwent planar (conventional) stress/redistribution thallium 201 scintigraphy twice (in a random crossover design). One study employed oral dipyridamole (300 mg) as the method of stress and the other study employed an intravenous infusion of adenosine as the method of stress. Dipyridamole stress imaging was performed in standard fashion and adenosine stress imaging was performed as described above. Again, the adenosine infusion was well tolerated in all subjects. The sensitivity, specificity and overall predictive accuracy for detection of coronary artery disease was 88.8%, 87.5% and 88.0%, respectively, with adenosine imaging, and 77.7%, 82.6% and 80.5%, respectively, with dipyridamole imaging. The positive predictive value of adenosine and dipyridamole imaging was 84.2% and 77.7% respectively. This study indicates that adenosine imaging is safe and may be superior to dipyridamole imaging for the accurate detection of angiographically significant coronary artery disease.

In the third set of experiments, 15 patients with angiographically documented coronary artery disease and 18 subjects with either angiographically normal coronary arteries (n=8) or healthy normal volunteers (n=10) underwent thallium 201 myocardial perfusion imaging using single photon emission computed tomography (SPECT). In all subjects, only an infusion of adenosine was employed as a method of stress. The adenosine infusion was initiated at 50 mcg/kg/min and titrated at 1 minute intervals by increments of 25 mcg/kg/min to a maximum dose of 140 mcg/kg/min. The maximum tolerable dose was maintained for at least 1 minute prior to and 3 minutes subsequent to a single bolus injection of thallium 201 (approximately 3.0 mCi). Early (stress) imaging was performed 5-10 minutes post-thallium and delayed (redistribution) imaging was performed 3-4 hours post-thallium. The SPECT images were acquired and reconstructed in standard fashion. Side effects occurred in 76% of the subjects, but were usually mild, did not require therapy and ceased instantly after discontinuing the adenosine infusion. Chest pain occurred in 53%, headache in 34% and cutaneous flushing in 15%. Dose-dependent decreases in systolic blood pressure (hypotension) and reflex increases in heart rate were common. Perfusion defects were detected during adenosine stress imaging in all 15 patients with known coronary artery disease and these defects were reversible in 9 (sensitivity = 100%). The adenosine stress images were interpreted as normal in 16 of 18 presumed healthy subjects (specificity = 89%). This study indi-

cates that adenosine-induced coronary vasodilation is a safe, convenient, and potent intervention to uncover perfusion defects during SPECT thallium scintigraphy in patients with coronary artery disease.

EXAMPLE II

As set forth in this example, the effects of intravenous adenosine as a pharmacological stressor in conjunction with echocardiography were evaluated.

Fifteen patients with a positive exercise (stress) SPECT thallium 201 tomogram were selected for this study. The tomographic perfusion defect was fixed (irreversible) in 6 subjects and reversible in 9 subjects. Subsequently, these patients underwent standard 2-dimensional echocardiographic studies under conditions of rest (baseline) and during an intravenous infusion of adenosine as previously described (Example I, 3rd set of experiments). Echocardiographic studies were performed over a 1 minute period prior to the adenosine infusion (baseline), during maximum adenosine infusion (140 mcg/kg/min), and 3 minutes after the cessation of the adenosine infusion. All echocardiographic studies included parasternal views (long axis and short axis at the level of the mitral valve, papillary muscles and apex) and apical views (4-chamber, 2-chamber and apical long axis). All echocardiographic images were interpreted by standard qualitative and quantitative techniques. The echocardiographic images obtained at rest were interpreted as normal in all subjects. However, left ventricular wall motion abnormalities were detected during adenosine (stress) studies in all 6 patients with fixed thallium perfusion defects. Left ventricular wall motion remained normal during the adenosine infusion in all patients with reversible thallium perfusion defects. This study indicates that adenosine may be a useful pharmacological stressor for the detection of ischemic ventricular dysfunction as assessed by echocardiography.

EXAMPLE III

As set forth in this example, the effects of intravenous and intracoronary adenosine as a pharmacological stressor in conjunction with measurements of coronary blood flow reserve (CBFR) were evaluated at the time of coronary arteriography using a Doppler flow catheter.

Ten patients with an angiographically normal left coronary artery were studied at the time of diagnostic coronary arteriography. A 3F Doppler catheter was positioned in the left coronary artery to measure coronary blood flow velocity (CBFV), and mean arterial pressure, heart rate and the ECG were simultaneously recorded. Following repeated measures of baseline CBFV, incremental doses of intracoronary papaverine (8-12 mg boluses), intracoronary adenosine (4-14 mcg boluses) and intravenous adenosine (70-140 mcg/kg/min infusions) were administered in crossover fashion. Each drug was titrated to the maximum coronary hyperemic response. While the ECG intervals were unchanged during adenosine administration, papaverine routinely prolonged the QT interval (mean 96 ± 18 msec). Relative to papaverine, maximum coronary hyperemic responses (4-5 fold increases in CBFV) were achieved with 14 mcg intracoronary bolus doses of adenosine, as well as 140 mcg/kg/min intravenous infusions of adenosine. Compared to papaverine, maximal coronary hyperemia occurred sooner with adenosine (10 vs 20 seconds) and resolved sooner with adeno-

sine (37 vs 118 seconds), consistent with its ultrashort half-life. This study indicates that maximal coronary hyperemia can be achieved with either intracoronary or intravenous adenosine and may be a useful technique to assess the vasodilatory reserve capacity (i.e., functional significance) of stenotic coronary vessels.

ADVANTAGES OF THIS INVENTION OVER CONVENTIONAL TECHNIQUES

Certainly, adenosine and the other analogs mentioned hereinabove as a pharmacological stressor have the advantage over exercise as a stressor in patients who are unable or are unwilling to exercise at a work load appropriate for the noninvasive assessment of coronary artery disease. It remains to be determined whether these compounds as a pharmacological stressor are superior to exercise as a stressor in the assessment of coronary artery disease among patients capable of exercising. Although no coronary vasodilators have been approved by the Food and Drug Administration for this indication, adenosine and the related compounds identified above possess several advantages over the other conventional agents such as, nitrates, papavarine, and dipyridamole. First, adenosine has an ultra short half-life (less than 20 seconds). As a result, its onset of action and clearance from the body are rapid and the time required to perform the procedure is shortened. Furthermore, side effects when they occur are rapidly controlled by reducing the infusion rate and rarely require discontinuing the infusion or treating with theophylline. Second, adenosine is an endogenous substance in humans and should not result in allergic reactions.

Having fully described the invention it is intended that it be limited solely by the lawful scope of the appended claims.

We claim:

1. A method of detecting the presence and assessing the severity of myocardial dysfunction in a human comprising the steps of:

- (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation; and
- (b) performing a technique on said human to detect the presence and assess the severity of said myocardial dysfunction.

2. A method of detecting the presence and assessing the severity of myocardial dysfunction in a human comprising the steps of:

- (a) administering by an intracoronary route to said human about 2 mcg to about 20 mcg of an adenosine receptor agonist sufficient to provide coronary artery dilation; and
- (b) performing a technique on said human to detect the presence and assess the severity of said myocardial dysfunction.

3. The method of claim 1 or 2, wherein said myocardial dysfunction is selected from the group consisting of coronary artery disease, ventricular dysfunction, and differences in blood flow through disease free coronary vessels and stenotic coronary vessels.

4. The method of claim 1 or 2, wherein said adenosine receptor agonist is selected from the group consisting of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide-adenosine, cyclopentyl adenosine, 2-chloro adenosine, adenine, inosine, adenosine monophosphate, adenosine diphosphate and adenosine triphosphate.

5. The method of claim 1 or 2, wherein said technique to detect the presence and assess the severity of myocardial dysfunction is selected from the group consisting of radiopharmaceutical myocardial perfusion imaging when said myocardial dysfunction is coronary artery disease, ventricular function imaging when said myocardial dysfunction is ventricular dysfunction and a method for measuring coronary blood flow velocity when said myocardial dysfunction is the difference in blood flow through disease free coronary vessels as opposed to stenotic coronary vessels.

6. The method of claim 1 wherein said adenosine receptor agonist is administered by intravenous infusion in a dosage of about 140 mcg/kg/minute.

7. The method of claims 1, 2 or 6, wherein said adenosine receptor agonist is adenosine.

8. The method of claim 3 wherein said adenosine receptor agonist is adenosine.

9. The method of claim 4 wherein said adenosine receptor agonist is adenosine.

10. The method of claim 1 wherein said radiopharmaceutical myocardial perfusion imaging is selected from the group consisting of scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET), nuclear magnetic resonance (NMR) imaging, perfusion contrast echocardiography, digital subtraction angiography (DSA) and ultrafast X-ray computed tomography (CINE CT).

11. The method of claim 10 wherein the radiopharmaceutical agent used in conjunction with said radiopharmaceutical myocardial perfusion imaging is selected from the group consisting of thallium-201, technetium-99m, derivatives of technetium-99m, nitrogen-13, rubidium-82 iodine-123 and oxygen-15.

12. The method of claim 11 wherein said radiopharmaceutical myocardial perfusion imaging technique is scintigraphy and said radiopharmaceutical agent is thallium-201.

13. The method of claim 5 wherein said ventricular function imaging technique is selected from the group consisting of echocardiography, contrast ventriculography and radionuclide angiography.

14. The method of claim 13 wherein said ventricular function imaging technique is echocardiography.

15. The method of claim 5 wherein said method for measuring coronary blood flow velocity is selected from the group consisting of doppler flow catheter, digital subtraction angiography and radiopharmaceutical imaging techniques.

16. The method of claim 15 wherein said method for measuring coronary blood flow velocity is doppler flow catheter.

17. A method of detecting the presence and assessing the severity of coronary artery disease in a human comprising the steps of:

- (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation
- (b) administering a radiopharmaceutical agent into said human; and
- (c) performing radiopharmaceutical myocardial perfusion imaging on said human in order to detect the presence and assess the severity of coronary artery disease.

18. The method of claim 17 wherein said adenosine receptor agonist is administered by intravenous infusion in a dosage of about 140 mcg/kg/minute.

19. A method of detecting the presence and assessing the severity of coronary artery disease in a human comprising the steps of:

- (a) administering by an intracoronary route to said human about 2 mcg to about 20 mcg of an adenosine receptor agonist sufficient to provide coronary artery dilation;
- (b) administering a radiopharmaceutical agent into said human; and
- (c) performing radiopharmaceutical myocardial perfusion imaging on said human in order to detect the presence and assess the severity of coronary artery disease.

20. The method of claim 17 or 19, wherein said adenosine receptor agonist is selected from the group consisting of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide-adenosine, cyclopentyl adenosine, 2-chloro adenosine, adenine, inosine, adenosine monophosphate, adenosine diphosphate and adenosine triphosphate.

21. The method of claim 17 or 19, wherein said radiopharmaceutical agent is selected from the group consisting of thallium-201, technetium-99m, derivatives of technetium-99m, nitrogen-13, rubidium-82 iodine-123 and oxygen-15.

22. The method of claim 17 or 19, wherein said radiopharmaceutical myocardial perfusion imaging is selected from the group consisting of scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET), nuclear magnetic resonance (NMR) imaging, perfusion contrast echocardiography, digital subtraction angiography (DSA) and ultrafast X-ray computed tomography (CINE CT).

23. The method of claim 17, 19 or 18, wherein said adenosine receptor agonist is adenosine.

24. The method of claim 20 wherein said adenosine receptor agonist is adenosine.

25. The method of claim 21 wherein said radiopharmaceutical agent is thallium-201.

26. The method of claim 22 wherein said radiopharmaceutical myocardial perfusion imaging is scintigraphy.

27. A method of detecting the presence and assessing the severity of ventricular dysfunction caused by coronary artery disease, in a human, comprising the steps of:

- (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation;
- (b) performing a ventricular function imaging technique on said human; and
- (c) determining the presence and assessing the severity of ventricular dysfunction.

28. A method of detecting the presence and assessing the severity of ventricular dysfunction caused by coronary artery disease, in a human, comprising the steps of:

- (a) administering by an intravenous route to said human about 2 mcg to about 20 mcg of an adenosine receptor agonist sufficient to provide coronary artery dilation;
- (b) performing a ventricular function imaging technique on said human; and
- (c) determining the presence and assessing the severity of ventricular dysfunction.

29. The method of claim 27 or 28, wherein said adenosine receptor agonist is selected from the group consisting of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide-adenosine, cyclopentyl adenosine,

2-chloro adenosine, adenine, inosine, adenosine monophosphate, adenosine diphosphate and adenosine triphosphate.

30. The method of claim 27 or 28, wherein said ventricular function imaging technique is selected from the group consisting of echocardiography, contrast ventriculography and radionuclide angiography.

31. The method of claim 27 wherein said adenosine receptor agonist is administered by intravenous infusion in a dosage of about 140 mcg/kg/minute.

32. The method of claim 27, 28 or 31, wherein said adenosine receptor agonist is adenosine.

33. The method of claim 29 wherein said adenosine receptor agonist is adenosine.

34. The method of claim 30 wherein said ventricular function imaging technique is echocardiography.

35. A method of determining the difference between the coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human comprising the steps of:

- (a) administering by an intravenous route to said human about 20 mcg/kg/minute to about 200 mcg/kg/minute of an adenosine receptor agonist sufficient to provide coronary artery dilation;
- (b) performing a method for measuring coronary blood flow velocity on said human in order to assess the vasodilatory capacity of disease free coronary vessels as opposed to stenotic coronary vessels.

36. The method of claim 35 wherein said adenosine receptor agonist is administered by intravenous infusion in a dosage of about 140 mcg/kg/minute.

37. A method of determining the difference between the coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human comprising the steps of:

- (a) administering by an intracoronary route to said human about 2 mcg to about 20 mcg of an adenosine receptor agonist sufficient to provide coronary artery dilation;
- (b) performing a method for measuring coronary blood flow velocity on said human in order to assess the vasodilatory capacity (reserve capacity) of disease free coronary vessels as opposed to stenotic coronary vessels.

38. The method according to claim 35 or 37, wherein said adenosine receptor agonist is selected from the group consisting of adenosine, 1-methyl-2-phenylethyl-adenosine, 5-ethyl carboxamide-adenosine, cyclopentyl adenosine, 2-chloro adenosine, adenine, inosine, adenosine monophosphate, adenosine diphosphate and adenosine triphosphate.

39. The method of claim 35 or 37, wherein said method for measuring coronary blood flow velocity is selected from the group of Doppler flow catheter, digital subtraction angiography and radiopharmaceutical imaging techniques.

40. The method of claim 35, 37 or 36, wherein said adenosine receptor agonist is adenosine.

41. The method of claim 38 wherein said adenosine receptor agonist is adenosine.

42. The method of claim 39 wherein said method for measuring coronary blood flow velocity is doppler flow catheter.

43. A method of detecting the presence and assessing the severity of coronary artery disease in a human comprising the steps of:

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- (a) administering to said human by intravenous infusion about 20 mcg/kg/minute to about 200 mcg/kg/minute of adenosine in order to provide coronary artery dilation;
- (b) administering thallium-201 to said human; and
- (c) performing the scintigraphy on said human in order to detect the presence and assess the severity of coronary artery disease.
44. A method of detecting the presence and assessing the severity of ventricular dysfunction in a human comprising the steps of:
- (a) administering to said human by intravenous infusion about 20 mcg/kg/minute to about 200 mcg/kg/minute of adenosine in order to provide coronary artery dilation;
- (b) performing an echocardiography on said human; and
- (c) determining the presence and assessing the severity of ventricular dysfunction.
45. A method of determining the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human comprising the steps of:
- (a) administering to said human by intracoronary bolus injection about 2 mcg to about 20 mcg of adenosine, in order to provide coronary artery dilation;
- (b) measuring the difference between coronary blood flow through disease-free coronary vessels and stenotic coronary vessels in said human using a doppler flow catheter in order to assess the vasodilatory capacity (reserve capacity) of disease-free coronary vessels as opposed to stenotic coronary vessels.

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46. A method of detecting the presence and assessing the severity of coronary artery disease in a human comprising the steps of:
- (a) administering to said human by intracoronary bolus injection about 2 mcg to about 20 mcg of adenosine in order to provide coronary artery dilation;
- (b) administering thallium-201 to said human; and
- (c) performing scintigraphy on said human in order to detect the presence and assess the severity of coronary artery disease.
47. A method of detecting the presence and assessing the severity of ventricular dysfunction in a human comprising the steps of:
- (a) administering to said human by intracoronary bolus injection about 2 mcg to about 20 mcg of adenosine in order to provide coronary artery dilation;
- (b) performing an echocardiography on said human; and
- (c) determining the presence and assessing the severity of ventricular dysfunction.
48. A method of determining the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels in a human comprising the steps of:
- (a) administering to said human by intravenous infusion about 20 mcg/kg/minute to about 200 mcg/kg/minute of adenosine, in order to provide coronary arter dilation;
- (b) measuring the difference between coronary blood flow through disease-free coronary vessels and stenotic coronary vessels in said human using a Doppler flow catheter in order to assess the vasodilatory capacity (reserve capacity) of disease-free coronary vessels as opposed to stenotic coronary vessels.
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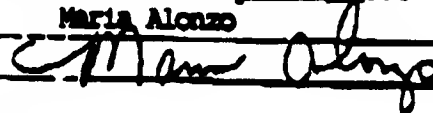
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Applicant: Mohiuddin et al.
Serial No.: 07/330,156
Filed: March 29, 1989
For: NOVEL METHOD OF MYOCARDIAL
Attorney: Jae H. Kim
File No.: 1541-006
Dated: April 7, 1995

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DIVISION
APR 11 1995

Adenosine for Injection - Major Activities
Use in Detecting and Assessing
the Severity of Myocardial Dysfunction
(IND 37,974 and NDA 20-059)

12/9/87	Investigational New Drug Application sent to FDA with protocol, "Adenosine as coronary vasodilator for use in exercise stress test before myocardial imaging in order to diagnose coronary artery disease."
12/10/87	FDA receipt of Investigational New Drug Application.
5/19/88	Submission of new protocol leading to assessing the usefulness of adenosine and diagnoses of coronary artery disease. This protocol uses cardiac catheterization in order to measure blood flow velocity during coronary vasodilation with papaverine and adenosine.
7/26/88	Response to comments and questions of FDA from letter dated 6/21/88.
10/6/88	Submission of results of completed toxicology studies noting no toxicological findings and a negative Ames test.
12/15/88	Submission of environmental impact analysis report.
6/2/89	Submission of two new protocols, protocol number C-5A, "Adenosine in conjunction with Thallium-20 cardiac imaging with GE tomographic equipment", and protocol number C-5B, "Adenosine in conjunction with Thallium-20 cardiac imaging with ADAC tomographic equipment".
6/7/89	Submission of amendment to IND for alternative techniques to cardiac imaging.
6/19/89	Meeting with FDA officials concerning placebo control study and Phase 2 studies needed for comparison of tomographic and angiographic procedures.
8/16/89	Submission of annual report for IND 30,974
2/1/90	Submission to FDA claiming new protocol entitled "A cross-over comparison of IV adenosine versus normal saline (placebo) in the non-invasive assessment of coronary artery disease a single photon emission computed tomography."
4/3/90	Submission of two new Phase 3 protocols and investigator information for IND 30,974.
2/9/90	New Drug Application 20,059 sent to FDA.
2/14/90	Date of receipt of NDA 20-059 by FDA.
4/19/90	FDA completes review of CMC and requests placing route of administration and sterility in description section of the package insert and suggests including target pH or pH range in container carton labels.

4/27/90	Response to letter dated 4/19/90
5/9/90	Submission of information relating to clinical studies, protocols, case report forms, list of investigators and patient enrollment.
8/17/90	Submission of amendment to add 30 ml container size.
9/14/90	Submission of protocol C-6, entitled "Open label study of adenoscan during non-invasive stress cardiac imaging in patients unable to exercise."
10/30/90	Submission of amendment showing twelve month stability data, specifically that adenosine 3 ml/mg as formulated, process and package will remain physically and chemically stable through 24 month expiration period at room temperature. Data from light study also included.
11/16/90	Submission of letter concerning status of NDA review.
11/29/90	Submission of updated bibliography on adenosine consisting of manuscripts and abstracts which have been published subsequent to original NDA submission on 2/13/90 and the adenosine safety update submitted on 6/30/90.
1/4/91	Submission of 1990 annual report for IND 30,974.
5/3/91	Telephone call from FDA relating to concerns about medical review.
5/8/91	Response to phone call of 5/3/91 about delayed adverse effects occurring 3-4 hours post-infusion; response states that patients are effectually observed for 4-5 hours post-infusion.
7/30/91	Receipt of FDA deficiency letter stating nine points that must be addressed, including, depyrogenation of vial stoppers, vial binder studies, product sterilization validation not being provided as well as container closure testing not being completed.
8/31/91	Response to deficiency letter of 7/30/91, all nine points addressed.
3/4/92	Submission to update stability data at both room temperature and accelerated data for 30 ml size product and update master batch records.
3/20/92	Receipt of FDA deficiency letter requesting further safety data concerning hypotension and hypertensive risk in patients with arrhythmia or bradycardia.
3/25/92	Receipt of FDA deficiency letter indicating there were no follow-up studies after administration of adenosine injection. Results must show effects after administration.
4/1/92	Meeting at FDA relating to safety issues.

4/29/92 Response to 3/20/92 deficiency letter wherein ten points are addressed. The CMC is amended to include stability and safety results as shown in the 24 hour period after administration. Data were presented on 1,067 consecutively enrolled new patients at recruiting centers from August '91 - March '92.

8/31/92 Submission of flow chart and complete batch records for all lots filed to the NDA in Section 3, Chemistry, Manufacturing and Control.

10/26/92 Submission of amendment for protocol C-6 which details the availability of the smaller package for use in trial (in addition investigator use in 3ml vials with 2ml fill).

12/3/92 Amendment to respond to the FDA about patent information.

2/19/93 Submission of response to 483 report (validity assessment) indicating that safety issues were previously addressed in April 29, 1992 amendment, and that the NDA should be ready for approval.

5/6/93 Telephone conference with FDA wherein FDA asked for comparative data between T-tube/port versus IV administration of adenosine.

5/7/93 Correspondence to FDA about allowing cross-referencing of IND 30,974 by a clinical investigator, to compare adenosine to nitric oxide in pre-transplant patients to determine which of these agents best predicts subsequent prognosis in patients with pulmonary hypertension.

5/12/93 Teleconference with FDA concerning status of review.

7/30/93 Submission of C-6 protocol, "An open label study of Adenoscan (intravenous adenosine) during non-invasive stress cardiac imaging in patients unable to exercise.

8/5/93 Receipt of manufacturing and control section review by Medco; FDA has recommended that testing sterility and pyrogens be added at two sites; requests updated batch records and updated vial size with labels.

8/10/93 Teleconference concerning questions about CMC.

8/20/93 Teleconference relating to the status of NDA review.

9/9/93 Teleconference initiated by FDA to understand Fujisawa USA, Inc.'s (licensee of U.S. Patent No. 5,070,877 and manufacturer of the adenosine product) procedure to assure there are no leachables from the filter that is used to introduced liquid into the vials of adenosine for injection.

10/9/93 Submission to FDA of safety profile in protocol C-6. The results show effects of adenosine for injection in 1,067 patients.

10/28/93 Teleconference initiated by FDA relating to labeling issues.

12/9/93	Telephone conference initiated by FDA to discuss labeling issues and update approval letter.
12/13/93	Receipt of approvable letter from the FDA indicating completed review of draft labeling and requesting final printed labeling and promotional materials.
2/8/94	Submission of final printed labeling for 3 mg/ml, 30 ml vial.
5/10/94	Teleconference initiated by FDA to disclose that Fujisawa USA, Inc.'s Grand Island plant was approved to manufacture adenosine on 4/6/94.
5/19/94	Received FDA comments on audit of Dr. Syed Mohiuddin's data by Office of Compliance that requests data analysis.
5/26/94	Communication to FDA to allow a clinical investigator to cross-reference NDA 20-059 and IND 30,974 and any amendments to submit IND for evaluating Adenoscan and myocardial salvage after acute myocardial infarction treated with primary angioplasty.
6/1/94	Response to FDA letter of May 19, 1994 upon review of protocol C-5A, there were no significant differences between any data sets compared to original data set of Dr. Mohiuddin.
6/8/94	Teleconference initiated by FDA about submission of NDA supplement with one month of stability data and to discuss filing of adenosine CMC supplement to add Abbott Laboratories as a manufacturer.
7/22/94	Submission of response to the May 18, 1994 deficiency letter.
8/4/94	Submission of twelve copies of the final printed label to FDA.
9/16/94	Teleconference initiated by the FDA indicating that the response submitted 7/22/94 was insufficient.
9/29/94	Teleconference initiated by FDA to discuss deficiencies related to environmental impact statement.
10/12/94	Submission of amendment to NDA to qualify Abbott Laboratories as manufacturer of adenosine for injection.
10/14/94	Submission of two sets of promotional launch campaign materials for Adenoscan (adenosine for injection).
10/28/94	Submission, in response to 10/12/94 letter, of updated information concerning a user fee contract.
11/30/94	Teleconference initiated by FDA thanking Medco for submission of proposed promotional materials.
1/11/95	Teleconference explaining Medco's statistical methods for confidence levels of the adenosine analysis.

1/24/95 **Withdrawal of October 12, 1994 amendment to NDA seeking Abbott Laboratories as manufacturer of adenosine product.**

4/17/95 **Teleconference relating to status of the environmental issues and release of "approvable" letter.**

4/18/95 **Teleconference initiated by FDA indicating that the division of drug marketing, advertising and communications would begin review of promotional materials.**

4/18/95 **Approvable letter sent by FDA.**

4/18/95 **Teleconference initiated by FDA regarding the environmental assessment issues described in the 4/18/95 approvable letter for adenosine for injection.**

4/20/95 **Submission to FDA relating to questions about environmental issues and certification from German authorities stating that adenosine is covered by the German plant certification.**

4/25/95 **Response to deficiencies noted in the approvable letter dated April 18, 1995 regarding specific environmental assessment issues.**

5/18/95 **Receipt of letter of approval from FDA.**